Chemotherapy Induced Nausea & Vomiting (CINV): What You Need to Know

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Presenter Disclosure

- **Faculty / Speaker's name:** James T. Paul

- **Relationships with commercial interests:**
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  - **Consulting Fees:** None.
  - **Other:** None.

Mitigating Potential Bias

- Not Applicable

Learning Objectives

1. Appreciate the impact chemotherapy Nausea & Vomiting has on patients and treatment
2. Review antiemetic options*

*Only discussing pharmacological options available on Formulary

Case 1 - Ms. Peters

- 56 year old woman. Newly diagnosed with Stage IV lung adenocarcinoma.
- PMHx: None. No medications. No allergies.
- Social: Never smoker, drinks ~3-4 beers/day
- Tx: Cisplatin ($75mg/m^2$) & Pemetrexed ($500mg/m^2$) q21days
- She is quite concerned about nausea & vomiting, as she remember her father 20 years ago, having significant vomiting with chemotherapy
- What anti-emetics will you prescribe?

Case 1 - Options

A. Dexamethasone & 5-HT_3
B. Dexamethasone & Dimenhydrinate (Gravol®)
C. Dexamethasone & 5-HT_3 & NK1
D. Dexamethasone & 5-HT_3 & NK1 & Olanzapine
E. Antiemetics not required

Case 2 - Mr. Roberts

- 62 year old man. Diagnosed with Stage III colon cancer, now resected
- PMHx: Hypertension Medications: HCTZ
- No allergies
- Social: Smoker (55 pack/years), no alcohol
- Booked for: FOLFOX (5-FU bolus 400mg/m^2 then 2,400mg/m^2, and oxaliplatin 85 mg/m^2)
- What anti-emetics will you prescribe?

Case 2 - Options

A. Dexamethasone & 5-HT_3
B. Dexamethasone & Dimenhydrinate (Gravol)
C. Dexamethasone & 5-HT_3 & NK1
D. Dexamethasone & 5-HT_3 & NK1 & Olanzapine
E. She doesn't need any antiemetics

Case 3 - Ms. Henderson

- 45 year old female. Recently had right sided mastectomy for a pT3N0 ductal carcinoma ER+ve PR+ve HER-2-ve
- PMHx: None. Medications: None. No allergies.
- Social: Never smoker, drinks 1 glass wine/day
- She tells you she gets nauseated easily when on boats, or a passenger in the car
- She is currently pre-cycle 3 of adjuvant TC
  - Docetaxel ($75 mg/m^2$), Cyclophosphamide ($600 mg/m^2$)

Case 3 - Ms. Henderson…continued

- She tells you, the nausea starts before she even walks into the cancer centre
  - It worsens when she enters the chemotherapy room, and the smell of hand wash exacerbates her nausea further
- Are you going to do anything differently for cycle 3?
- She is currently taking dexamethasone 4mg PO BID, 5-HT_3

Case 3 - Options

A. Do nothing
B. Add a NK1 receptor antagonist
C. Add anxiolytic 30 minutes prior to chemotherapy
D. Ask her to double her dexamethasone dose

Case 4 - Ms. Smith

- 59 yr female, resected pT_2N_1 RLL adenocarcinoma
- PMHx: None. Medication: None. Allergies: None.
- Social: Ex-smoker, quit 1 year ago (55 pack years)
- Adj. Carboplatin & Vinorelbine x 1 cycles
- She had terrible vomiting after her 1st cycle and required a visit to your CCPN with IV hydration
- You review her existing medications: dexamethasone, 5-HT3, metoclopramide prn
  - You decided to add NK1 to her existing antiemetic regime. What else must you do?

Case 4 - Options

A. Do nothing
B. Double her dexamethasone dose
C. Increase total duration of 5-HT_3
D. Half her dose of dexamethasone
E. Ask her to avoid eating prior to chemotherapy

Definitions

- Nausea
  - A non-specific symptom, with the general sense of uneasiness and discomfort in the upper stomach with an involuntary urge to vomit
- Vomiting
  - Ejection of matter from the stomach in retrograde fashion through the esophagus and mouth

Impact of Nausea & Vomiting

- Adversely affects quality of life, make it difficult to perform activities of daily living, medical complications, treatment discontinuation
- Increased costs:
  - Increased visits to clinics and Emergency Rooms
  - Estimated that poorly controlled CINV may increase monthly health care costs upwards of $1,300/per individual/month (US data)
  - Inability to work

Shih, YCT et al. Cancer. 110;2007

Not to be minimized

- Chemotherapy associated nausea & vomiting is the most feared side effect of cancer treatment
- With highly emetogenic chemotherapy in 1970s patients would vomit 5-25 times (average 10.5 times) in first 24 hours
- Modern (2003) antiemetics have improved incidence, 32.8% acute CINV, 60.7% delayed CINV

Gralla RJ et al. NEJM. 305;1981
Ihbe-Heffinger et al. Annals of Oncology 15; 2004

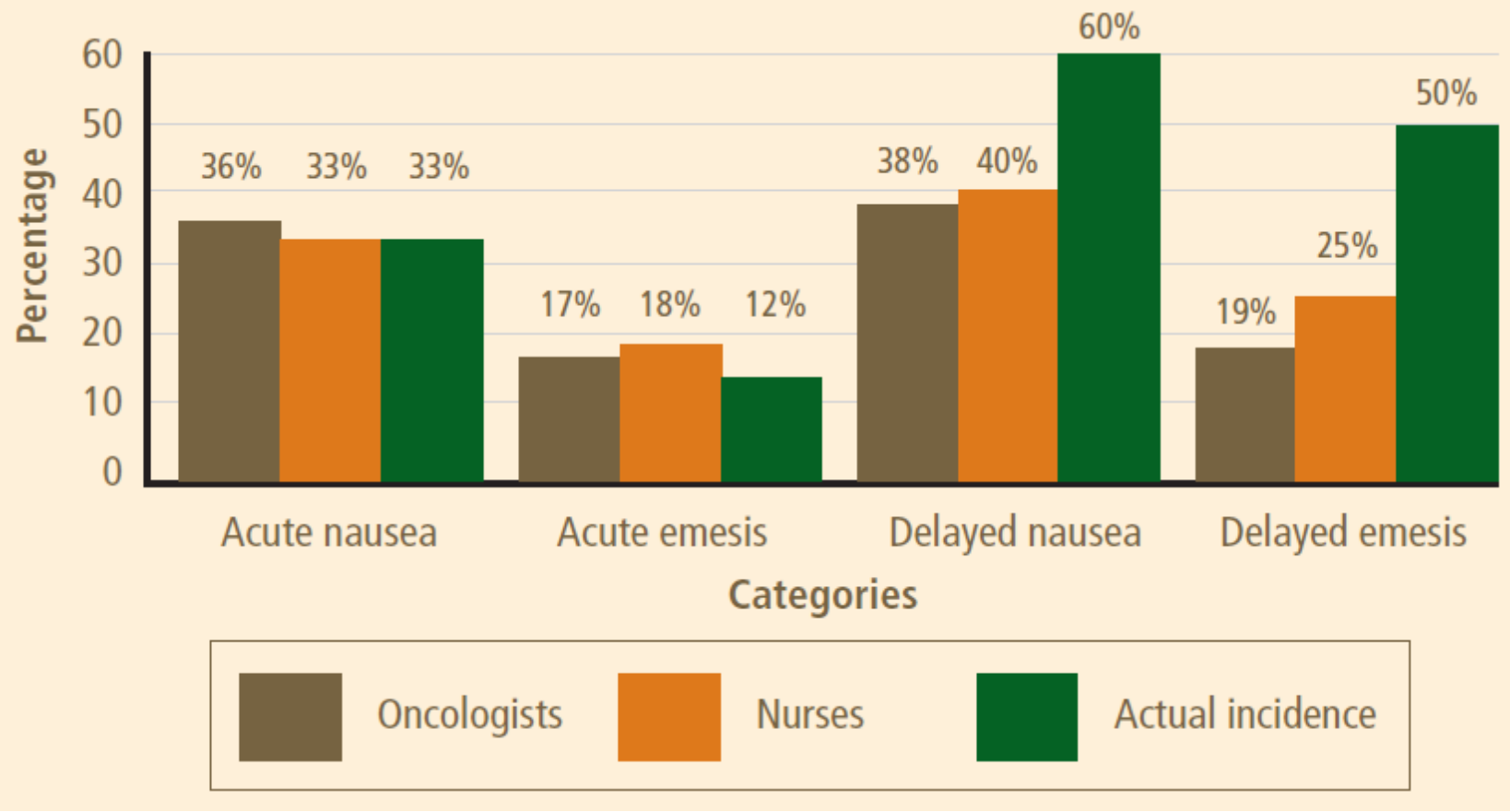
Health Care Providers

- More than 50% of patients did not receive an antiemetic regimen that was in accordance of ASCO guidelines (2004)
  - Followed guidelines – 49.5% delayed CINV
  - Did not receive appropriate tx – 71.6% delayed CINV

- Since this study there have been the introduction of additional antiemetic options

Ihbe-Heffinger et al. Annals of Oncology 15; 2004

Prediction vs Actual Incidence of CINV



Hawkins, R et al. Clinical Journal of Oncology Nursing. 13; 2009.

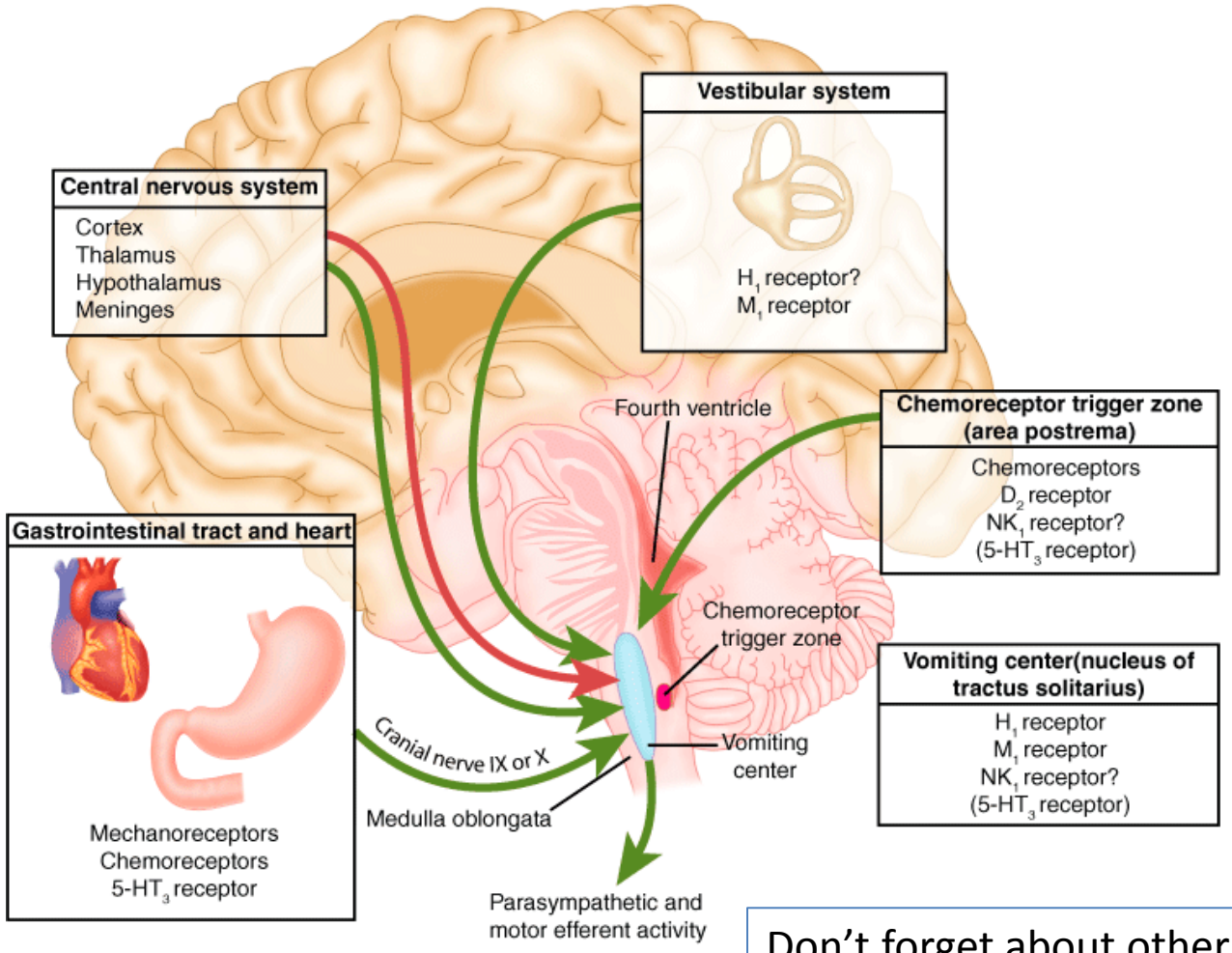
Area Postrema

- Chemotherapy drugs can activate neurotransmitter receptors that are present in the area postrema of the brain
- Detects toxins in the blood & acts as a vomiting inducing centre
- Is a critical homeostatic integration center for humoral and neural signals
- It is a densely vascularized structure that lacks tight junctions between endothelial cells, thereby allowing it to detect various toxins in the blood as well as in the cerebrospinal fluid

The Players

- Dopamine
- Serotonin
- Substance P
- Others?

Differential Diagnosis



Source: Katzung BG, Masters SB, Trevor AJ: *Basic & Clinical Pharmacology, 11th Edition:* http://www.accessmedicine.com

Don't forget about other possible etiologies for nausea & vomiting

Two Pathways

- Peripheral pathway
  - Activated within 24 hours after chemotherapy
  - Acute emesis occurring 0 – 24 hours after chemotherapy
- Central pathway
  - Activated after 24 hours after chemotherapy
  - Delayed emesis occurring 1 – 5 days after chemotherapy
  - Can also induce acute chemotherapy-induced emesis

Factors Influencing Nausea & Vomiting with Chemotherapy

- Emetogenic potential of the chemotherapy
- Failure by practitioner to initiate appropriate initial tx
- Patient factors
  - Compliance
  - Age <55 years
  - Female sex
  - History of Nausea & Vomiting
  - Impaired quality of life
  - No history of alcohol use
  - Anxiety
  - Fatigue
  - Motion sickness

Emetic Risk of IV Antineoplastic Agents

Emetogenic Potential	Chemotherapy	
High (>90%)	Cisplatin Anthracycline/cyclosphamide combination	Dacarbazine
Moderate (>30 – 90%)	Alemtuzumab Carboplatin Doxorubicin Epirubicin	Irinotecan Oxaliplatin Temozolomide
Low (10 – 30%)	Aflibercept Bortezomib Etoposide Cetuximab 5-Fluorouracil	Gemcitabine Paclitaxel Panitumumab Pemetrexed Topotecan
Minimal (0 - 10%)	Bevacizumab Fludarabine Nivolumab Ofatumumab	Pembrolizumab Rituximab Trastuzumab Vinorelbine

Roila F. et al. Annals of Oncology. 27; 2016

Types of Chemotherapy-Induced Nausea & Vomiting

Classification	Definition
Acute	Occurs within first 24 hours after initiation of chemotherapy, peaks 5-6 hours
Delayed	Occurs 24 hours to 2-5 days after chemotherapy
Breakthrough	Occurring despite appropriate prophylactic treatment
Anticipatory	Occurring before a treatment as a conditioned response to the occurrence of chemotherapy induced nausea and vomiting in previous cycles
Refractory	Recurring in subsequent cycles of therapy, (excluding anticipatory nausea & vomiting)

Treatment

- Proactive, rather than reactive treatment for CINV is preferred

Where Have We Come From?

The New England
Journal of Medicine

Volume 305 OCTOBER 15, 1981 Number 16

ANTIEMETIC EFFICACY OF HIGH-DOSE METOCLOPRAMIDE: RANDOMIZED TRIALS WITH PLACEBO AND PROCHLORPERAZINE IN PATIENTS WITH CHEMOTHERAPY-INDUCED NAUSEA AND VOMITING

Richard J. Gralla, M.D., Loretta M. Itri, M.D., Sharon E. Pisko, R.N., Anna E. Squillante, R.N., David P. Kelsen, M.D., David W. Braun, Jr., Ph.D., Laurie A. Bordin, R.N., Thomas J. Braun, M.D., and Charles W. Young, M.D.

- Metoclopramide
  - 2mg/kg dose (!!)
  - 30 min prior, 1.5 hrs, 3.5 hrs, 5.5 hrs, 8.5 hrs

	METOCLO-PRAMIDE (n = 11)	PLACEBO (n = 10)	P
No. of emetic episodes			
Median	1	10.5	0.001
Range	0–9	5–25	
Volume of emesis (ml)			
Median	20	404	0.001
Range	0–225	250–1870	
Duration of nausea (hr)			
Median	0	3.7	0.042
Range	0–16.2	0–19.2	
Duration of vomiting (hr)			
Median	0.2	3.6	0.028
Range	0–16.8	2–17.0	

Dexamethasone

- Aapro MS, Alberts DS. High-dose dexamethasone for prevention of cis-platin induced vomiting. Cancer Chemotherapy Pharmacology. 1981;7:11.

- Aapro MS et al. Double-blind crossover study of the antiemetic efficacy of high-dose dexamethasone versus high-dose metoclopramide. Journal of Clinical Oncology. 1984.
  - Demonstrated equal efficacy, but improved side-effect profile and preference for dexamethasone.

5-HT_3-Receptor Antagonists 1st Generation

- Selective 5-HT_3-receptor antagonist, blocking serotonin:
  - Peripherally on vagal nerve terminals
  - Centrally in the chemoreceptor trigger zone
    - Ondansetron - 1991
    - Granisetron - 1997
    - Dolasetron – 1997

5-HT_3-Receptor Antagnoists

- Ondansetron - 1991
- Granisetron - 1997
- Dolasetron - 1997

- Granisetron vs Ondansetron
  - Navari RM et al. JCO. 1995.
- Ondansetron vs Granisetron
  - Italian Group for Antiemetic Research. Annals Oncology 1995.
- Dolasetron vs Ondansetron
  - Hesketh P et al. JCO. 1996

Support Care Cancer (2007) 15: 1023–1033
DOI 10.1007/s00520-006-0186-7

REVIEW ARTICLE

K. Jordan
A. Hinke
A. Grothey
W. Voigt
D. Arnold
H.-H. Wolf
H.-J. Schmoll

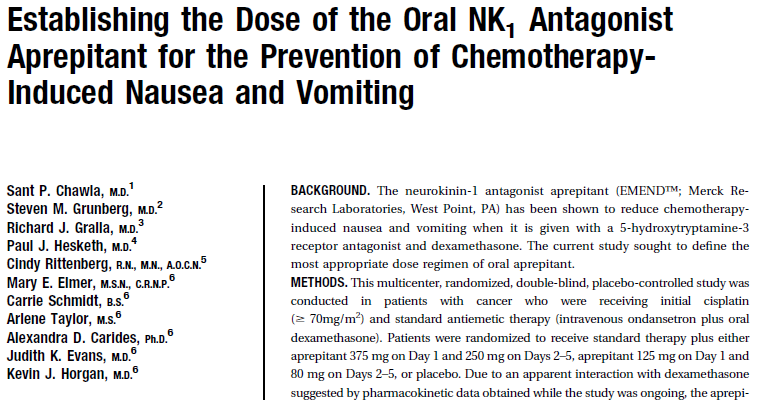
A meta-analysis comparing the efficacy of four 5-HT3-receptor antagonists for acute chemotherapy-induced emesis

NK_1-Receptor Antagonists

- Antagonist targeting NK_1 receptors for substance P
- Aprepitant was the first NK_1-receptor antagonist approved – 2003
- Fosaprepitant
  - A prodrug & IV form of aprepitant
  - Similar outcomes compared to aprepitant

Aprepitant

- Comes as Tri-pack
  - 125 mg, 80 mg, 80 mg
- Can inhibit CYP3A4
- Therefore, a <u>reduced dose of dexamethasone</u> (CYP3A4 substrate) should be used with aprepitant



Establishing the Dose of the Oral NK_1 Antagonist Aprepitant for the Prevention of Chemotherapy-Induced Nausea and Vomiting

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BACKGROUND. The neurokinin-1 antagonist aprepitant (EMEND™; Merck Research Laboratories, West Point, PA) has been shown to reduce chemotherapy-induced nausea and vomiting when it is given with a 5-hydroxytryptamine-3 receptor antagonist and dexamethasone. The current study sought to define the most appropriate dose regimen of oral aprepitant.

METHODS. This multicenter, randomized, double-blind, placebo-controlled study was conducted in patients with cancer who were receiving initial cisplatin (≥ 70mg/m^2) and standard antiemetic therapy (intravenous ondansetron plus oral dexamethasone). Patients were randomized to receive standard therapy plus either aprepitant 375 mg on Day 1 and 250 mg on Days 2–5, aprepitant 125 mg on Day 1 and 80 mg on Days 2–5, or placebo. Due to an apparent interaction with dexamethasone suggested by pharmacokinetic data obtained while the study was ongoing, the aprepi-

Chawla SP et al Cancer 97;2003

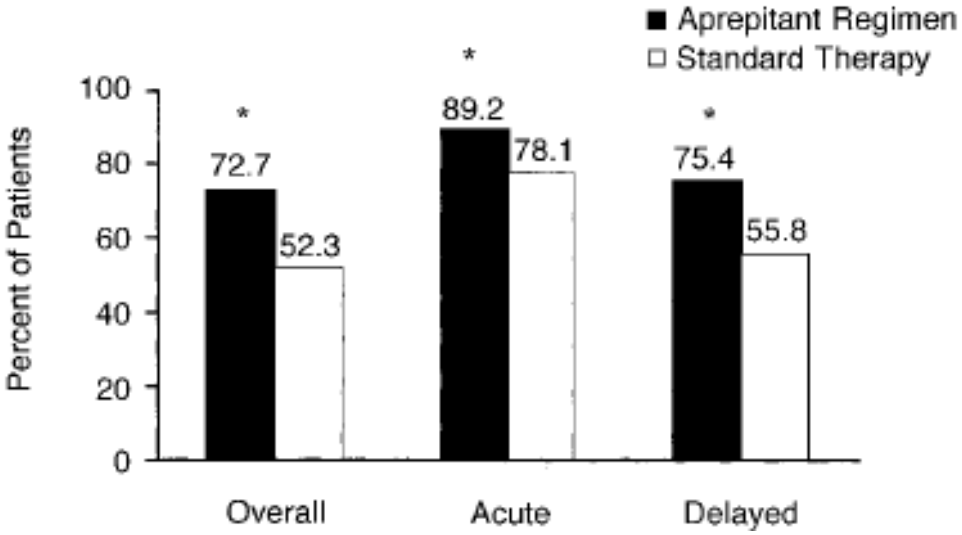
The Oral Neurokinin-1 Antagonist Aprepitant for the Prevention of Chemotherapy-Induced Nausea and Vomiting: A Multinational, Randomized, Double-Blind, Placebo-Controlled Trial in Patients Receiving High-Dose Cisplatin—The Aprepitant Protocol 052 Study Group

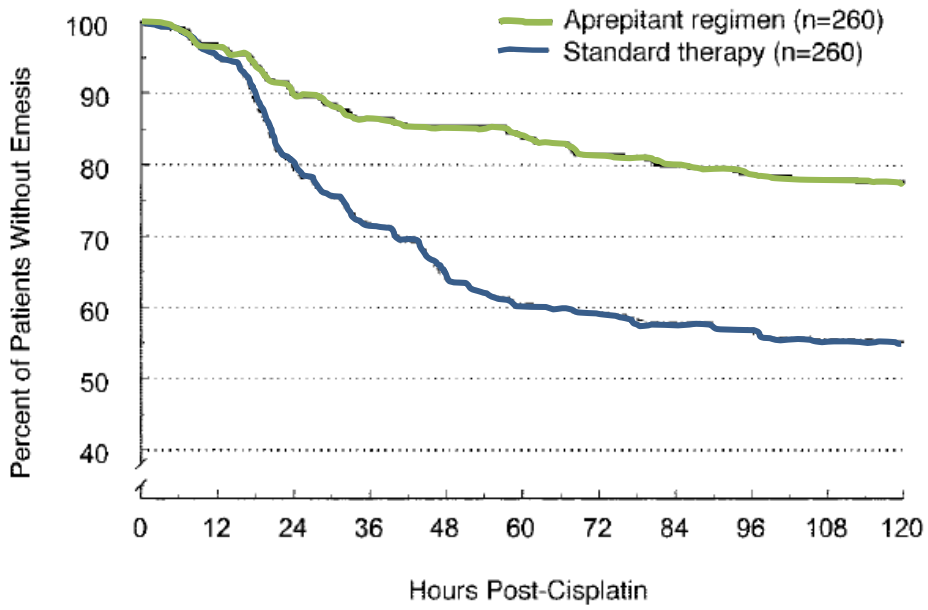
By Paul J. Hesketh, Steven M. Grunberg, Richard J. Gralla, David G. Warr, Fausto Roila, Ronald de Wit, Sant P. Chawla, Alexandra D. Carides, Juliana Ianus, Mary E. Elmer, Judith K. Evans, Klaus Beck, Scott Reines, and Kevin J. Horgan

- Cisplatin > 70mg/m^2
- Control:
  - At time of chemotherapy: Ondansetron x 1, dexamethasone x1
  - Outpatient: Dexamethasone BID days x 3 days
- Study:
  - At treatment: Aprepitant, ondansetron x 1, dexamethasone x 1,
  - Outpatient: Aprepitant OD x 2 d. and dexamethasone OD x 3 d.

Hesketh, PJ et al. JCO. 21; 2003.

Results


Aprepitant Regimen
Standard Therapy
Percent of Patients
100
80
60
40
20
0
*
72.7
52.3
*
89.2
78.1
*
75.4
55.8
Overall
Acute
Delayed


Aprepitant regimen (n=260)
Standard therapy (n=260)
Percent of Patients Without Emesis
100
90
80
70
60
50
40
0
12
24
36
48
60
72
84
96
108
120
Hours Post-Cisplatin

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Olanzapine for the Prevention of Chemotherapy-Induced Nausea and Vomiting

- Double blind, phase III trial
- Experimental: Olanzapine + 5-HT_3 + DEX + NK_1
- Control: Placebo + 5-HT_3 + DEX + NK_1
- Eligible chemo: Cisplatin (≥70 mg/m^2) or doxorubicin (60 mg/m^2) + cyclophosphamide (600 mg/m^2)

Navari RM et al. NEJM. 375; 2016

Control of Nausea

Variable	Olanzapine (N=192)	Placebo (N=188)	Total (N=380)	P Value*	Adjusted P Value†
	number/total number (percent)				
0–24 hr after chemotherapy					
No nausea	135/183 (73.8)	82/181 (45.3)	217/364 (59.6)	<0.001	0.002
Nausea	48/183 (26.2)	99/181 (54.7)	147/364 (40.4)		
25–120 hr after chemotherapy					
No nausea	75/177 (42.4)	45/177 (25.4)	120/354 (33.9)	0.001	0.002
Nausea	102/177 (57.6)	132/177 (74.6)	234/354 (66.1)		
0–120 hr after chemotherapy					
No nausea	66/177 (37.3)	39/178 (21.9)	105/355 (29.6)	0.002	0.002
Nausea	111/177 (62.7)	139/178 (78.1)	250/355 (70.4)		

Breakthrough CINV

- Use maximally effective antiemetics as first-line treatment rather than a ‘use later’, if required approach
- Available evidence (limited) for breakthrough CINV suggests the use of an antiemetic with a different mechanism of action than that of the antiemetics used for prophylaxis

Anticipatory Nausea

- Key is prevention of CINV with initial cycles
- Very little trial data available
- Focus has been on cognitive based therapies, and benzodiazepines
  - Muscle relaxation training, Systemic desensitisation, Hypnosis
  - Alprazolam, Lorazepam

Greenberg DB et al. Cancer Treat Reports. 71; 1987
Razavi D et al. JCO. 11; 1993.
Malik IA et al. American Journal of Clinical Oncology. 18; 1995.

So what does this all mean?

Guideline Recommendations

Risk Category	Dose on Chemotherapy Day (choose one agent from each category)		Dosing on Subsequent Days
High Risk >90%	1	Aprepitant 125 mg (NK_1)	Aprepitant 80 mg daily x 2 days Dexamethasone 4 mg daily x 3 days Olanzapine 10 mg daily x 3 days
	2	Ondansetron 16 mg (5-HT_3)	
	3	Dexamethasone 8 mg	
	4	Olanzapine 10 mg	
Moderate Risk 31-90%	1	Ondansetron 16 mg (5-HT_3)	Dexamethasone 4 mg BID x 2 days Metoclopramide 10-20 mg PO q4h prn or Prochlorperazine 10 mg PO q6h prn
	2	Dexamethasone 12 mg	
Low Risk 10-30%	1	Dexamethasone 12 mg	Nothing routinely. Metoclopramide 10-20 mg PO q4h prn or Prochlorperazine 10 mg PO q6h prn
Minimal Risk <10%	1	Nothing routinely	

Note: There may be some variability in the Ondansetron, and Dexamethasone dose on day of chemotherapy.

Modified from: CCO. Antiemetic Working Group. Antiemetic Report. October 2013.
Hesketh PJ et al. JCO. 34; 2016.
Roila F. et al. Annals of Oncology. 27; 2016.

Case 1 - Ms. Peters

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- Tx: Cisplatin ($75mg/m^2$) & Pemetrexed ($500mg/m^2$) q21days
- She is quite concerned about nausea & vomiting, as she remember her father 20 years ago, having significant vomiting with chemotherapy
- What anti-emetics will you prescribe?

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B. Dexamethasone & Dimenhydrinate (Gravol®)
C. Dexamethasone & 5-HT_3 & NK1
D. Dexamethasone & 5-HT_3 & NK1 & Olanzapine
E. Antiemetics not required

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A. Dexamethasone & 5-HT_3
B. Dexamethasone & Dimenhydrinate (Gravol®)
C. Dexamethasone & 5-HT_3 & NK1
D. Dexamethasone & 5-HT_3 & NK1 & Olanzapine
E. Antiemetics not required

Suggestions

- Review chemotherapy
  - Cisplatin – high emetic risk
  - Pemetrexed – low emetic risk
- Guidelines would recommend 4 antiemetic agents
- Don't forget:
  - Olanzapine should not be used with metoclopramide (Extrapyramidal reaction risk, or neuroleptic malignant syndrome)
  - Recommend not to use metoclopramide. Use prochlorperazine prn (level C interaction – Anticholinergic) with olanzapine

High Risk >90%	**1**	**Aprepitant 125 mg (NK_1)**	**Aprepitant 80 mg daily x 2 days Dexamethasone 4 mg daily x 3 days Olanzapine 10 mg daily x 3 days**
	2	Ondansetron 16 mg ($5\text{-}HT_3$)	
	3	Dexamethasone 8 mg	
	4	Olanzapine 10 mg	

Case 2 - Mr. Roberts

- 62 year old man. Diagnosed with Stage III colon cancer, now resected
- PMHx: Hypertension Medications: HCTZ
- No allergies
- Social: Smoker (55 pack/years), no alcohol
- Booked for: FOLFOX (5-FU bolus 400mg/m^2 then 2,400mg/m^2, and oxaliplatin 85 mg/m^2)
- What anti-emetics will you prescribe?

Case 2 - Options

A. Dexamethasone & 5-HT_3
B. Dexamethasone & Dimenhydrinate (Gravol)
C. Dexamethasone & 5-HT_3 & NK1
D. Dexamethasone & 5-HT_3 & NK1 & Olanzapine
E. She doesn't need any antiemetics

Case 2 - Options

A. **Dexamethasone & 5-HT_3**
B. Dexamethasone & Dimenhydrinate (Gravol)
C. Dexamethasone & 5-HT_3 & NK1
D. Dexamethasone & 5-HT_3 & NK1 & Olanzapine
E. She doesn't need any antiemetics

Suggestions

- Review chemotherapy
  - 5-Fluororuracil – low emetic risk
  - Irinotecan – moderate emetic risk
- Applicable risk factors for CINV – age, sex, ethanol history
- Anti-emetic regime is based on greatest emetic risk

Moderate Risk 31-90%	**1**	**Ondansetron 16 mg ($5\text{-}HT_3$)**	**Dexamethasone 4 mg daily BID x 2 days Metoclopramide 10-20 mg PO q4h prn or Prochlorperazine 10 mg PO q6h prn**
	2	Dexamethasone 12 mg	

Case 2 - Mr. Roberts continued

- He reports having good CINV control for the first 24 hours, then began having retching, and inability to eat anything. He maximized his metoclopramide without much help.
- He denies history of headaches, vision changes, unilateral weakness, or difficulty with ambulation.
- He is now pre-cycle 2. What would you do at this point?

Suggestions

- Likely breakthrough nausea and vomiting
- Limited evidence to guide
  - Further history of timing of nausea & vomiting?
    - ?After current antiemetics completed?
- Adding agent which acts by different mechanism likely suggested

Case 3 - Ms. Henderson

- 45 year old female. Recently had right sided mastectomy for a pT3N0 ductal carcinoma ER+ve PR+ve HER-2-ve
- PMHx: None Medications: None. No allergies.
- Social: Never smoker, drinks 1 glass wine/day
- She tells you she gets nauseated easily when on boats, or a passenger in the car
- She is currently pre-cycle 3 of adjuvant TC
  - Docetaxel ($75 mg/m^2$), Cyclophosphamide ($600 mg/m^2$)

Case 3 - Ms. Henderson…continued

- She tells you, the nausea starts before she even walks into the cancer centre
  - It worsens when she enters the chemotherapy room, and the smell of hand wash exacerbates her nausea further
- Are you going to do anything differently for cycle 3?
- She is currently taking dexamethasone 4mg PO BID, 5-HT_3

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A. Do nothing
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C. Add anxiolytic 30 minutes prior to chemotherapy
D. Ask her to double her dexamethasone dose

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Suggestions

- Review chemotherapy
  - Docetaxel – low emetic risk
  - Cyclophosphamide – moderate emetic risk
- Review antiemetic medications, and how she is taking them
- History suggests anticipatory CINV
- Avoid visual queues (different nurse, private room), avoid scents (hospital food, alcohol hand wash)
- Premedicate: Benzodiazepine

Case 4 - Ms. Smith

- 59 yr female, resected pT_2N_1 RLL adenocarcinoma
- PMHx: None Medication: None Allergies: None
- Social: Ex-smoker, quit 1 year ago (55 pack years)
- Adj. Carboplatin & Vinorelbine x 1 cycles
- She had terrible vomiting after her 1st cycle and required a visit to your CCPN with IV hydration
- You review her existing medications: dexamethasone, 5-HT3, metoclopramide prn
  - You decided to add NK1 to her existing antiemetic regime. What else must you do?

Case 4 - Options

A. Do nothing
B. Double her dexamethasone dose
C. Increase total duration of 5-HT_3
D. Half her dose of dexamethasone
E. Ask her to avoid eating prior to chemotherapy

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- Aprepitant
  - Inhibits CYP3A4
    - Therefore, a reduced dose of dexamethasone (CYP3A4 substrate) should be used with aprepitant

Chawla SP et al Cancer 97;2003

Available Resources

- Antiemetic Working Group. Antiemetic Report for Clinical Evidence for Recommendations. Cancer Care Ontario. October 2013.

- Basch E, et al. Antiemetics: American Society of Clinical Oncology Clinical Practice Guideline Update. Journal of Clinical Oncology. 2011.
  - ASCO Focused Guideline Update. February 2016.

- Roila F. et al. 2016 MASCC and ESMO Guideline Update for the Prevention of Chemotherapy…in Advanced Cancer Patients. Annals of Oncology 2016.

Take home message(s)

- Impact of CINV is greater than appreciated
- Review antiemetic medications with patients

Questions?